

REMARKS

In the Non-Final Official Action dated July 8, 2011, Claims 28, 29 and 32-37 are rejected under 35 U.S.C. §103(a) as being obvious over Batkai et al. in view of U.S. 5,624,941 (Barth) and U.S. 6,143,752 (Oren).

This response addresses the sole remaining rejection. Favorable reconsideration of the pending claim is respectfully requested in view of the following remarks. At the outset, Applicants, through the undersigned wish to thank Examiner Bori for the courtesy and assistance provided in connection with a telephonic interview conducted on November 7, 2011.

As noted above, Claims 28, 29 and 32-37 are rejected under 35 U.S.C. §103(a) as allegedly unpatentable over Batkai et al. in view of U.S. 5,624,941 (Barth) and U.S. 6,143,752 (Oren). In response and in an effort to expedite favorable prosecution on the merits, Claim 28 has been amended and Claims 20 and 29-37 have been cancelled, without prejudice. Support for the amendment to Claim 28 is found at p. 10, lines 25-26, no new matter has been added and no further search is believed to be needed.

The invention, embodied in Claim 28, is directed to a method of reducing hepatic fibrosis in a mammal in need thereof which comprises administering a therapeutically effective amount of at least one CB1 receptor antagonist. The Examiner acknowledges that Batkai fails to disclose a method of treating hepatic fibrosis by using SR141716A, but refers to the increase of CB1 receptors in cirrhotic livers, as mentioned in the abstract.

However, the Examiner has apparently overlooked the subsequent sentence in the abstract of Batkai:

These results implicate [...] vascular CB1 receptors in the vasodilator state in advanced cirrhosis and indicate a novel approach for its management. (emphasis added)

Batkai simply does not teach or suggest any reduction of hepatic fibrosis whatsoever.

Barth does not even address the treatment of hepatic diseases. Barth teaches treating diseases pertaining to the immune system, the central nervous system and the cardiovascular or endocrine system, such as: thymic disorders, vomiting, myorelaxation, various types of neuropathy, memory disorders, dyskinesia, migraine, asthma, epilepsy, glaucoma, cancer, ischemia and and/or, orthostatic hypotension and cardiac insufficiency (col. 1, 1. 45-61).

Oren relates to the treatment of infectious hepatic diseases such as parasitic or viral hepatitis, or of autoimmune hepatic diseases, by inducing a hypothyroid condition in a patient.

The Examiner refers to the following quote from Oren:

Pathologically, cirrhosis is defined as extensive fibrosis in the liver, the end-stage of fibrosis is cirrhosis

Applicants agree that the end-stage of fibrosis is cirrhosis. However, the aim of the claimed method is to avoid reaching this end-stage, namely reducing hepatic fibrosis, which is not suggested in Batkai or Oren.

Applicants wish to reemphasize that the present invention is not the mere discovery of a mechanism of action which would explain an effect already observed in the prior art. Quite to the contrary, the present invention constitutes a novel application of antagonists of the CB1 receptor based on the heretofore unappreciated and unsuggested novel technical effect: the reduction of fibrosis.

The existence of this novel technical effect leads to a spectrum of unique applications, which are distinct from those of the prior art.

In the present case, the invention provides, *inter alia*, that antagonists of the CB1 receptor reduce hepatic fibrosis which is an early stage of many forms of liver injury. Hepatic fibrosis is not cirrhosis.

Batkai et al. disclose that antagonists of the CB1 receptor may be used for decreasing the elevated mesenteric blood flow and portal pressure observed in cirrhosis, which is the end stage of many forms of liver injury. The prior art thus teaches that antagonists of the CB1 receptor reduce vasodilation in cirrhosis.

The use of antagonists of the CB1 receptor according to the present invention relies therefore on a distinct effect and targets a different population of patients, in order to treat a different spectrum of pathologies. Hepatic fibrosis is differentiated from cirrhosis and the reduction of hepatic fibrosis is patentably distinct.

Batkai et al. disclose the presence of CB1 receptor in endothelial cells isolated from hepatic arteries and their increased expression during cirrhosis. More particularly, Batkai et al. relate to advanced liver cirrhosis, namely the last step of cirrhosis, and to the activity of endocannabinoids as ligands of vascular CB1 receptors on the vasodilated state resulting from this advanced liver cirrhosis.

Nowhere does Batkai et al. teach or suggest that cirrhosis and the resulting vasodilated state are connected to a reduction in hepatic fibrosis-as presently claimed.

Batkai et al. mention on p. 830, left column, 2nd paragraph, that “...*SR141716A treatment was able to significantly reduce the markedly elevated mesenteric blood flow and portal venous pressure of the cirrhotic animals*”.

Thus, all the results shown in Batkai et al. relate to altered blood flow during advanced liver cirrhosis and to the resulting increased blood pressure. Accordingly, Batkai et al.

only pertains to a symptom of cirrhosis, namely a mechanism of action which leads to a severe alteration, even death, of the liver.

However, there is no suggestion of any link between hepatic fibrosis and cirrhosis in Batkai et al.

As stated on p. 831, end of left column:

“The present findings suggest that this elusive mediator might be an endocannabinoid acting at vascular CB1 receptors, and antagonists of these receptors might offer a therapeutic approach to the management of patients with advanced liver cirrhosis awaiting liver transplantation” (emphasis added).

This passage clearly shows that the use of CB1 antagonists in Batkai et al. is suggested to be used to address very late stage cirrhosis.

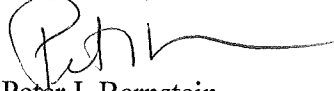
On the contrary, the subject-matter of present invention is to reduce hepatic fibrosis at a very early stage, to avoid the type of treatment referred to in Batkai et al. Thus, Batkai et al. can, at best, be viewed as a clear teaching away from the claimed invention.

Accordingly, the rejection of Claims 28, 29 and 32-37 under 35 U.S.C. §103(a) is overcome and withdrawal thereof is respectfully requested.

Wherefore, it is earnestly believed the instant application is in condition for allowance, passage to which is earnestly solicited.

Should the Examiner have any questions or wish to discuss any of the above or this case otherwise, they are invited to contact the undersigned as indicated.

Respectfully submitted,

A handwritten signature in black ink, appearing to read 'P. Bernstein', with a long horizontal flourish extending to the right.

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